WARTHIN (A. S.)

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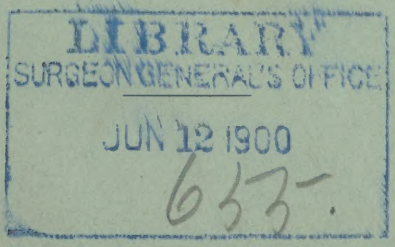

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THE DIAGNOSIS OF PRIMARY SARCOMA OF THE PLEURA FROM THE CELLS FOUND IN THE PLEURITIC EXUDATE.

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THE microscopic examination of the sediment of pleural and peritoneal effusions for the purpose of establishing the diagnosis of new growths of these membranes before a clinical diagnosis can be determined is a diagnostic measure but rarely instituted, if the scantiness of the literature upon the subject is to be taken as an index. Much has been done with the chemistry of these fluids, but few careful investigations have been reported of the cellular constituents in those cases in which malignant tumors of the pleura or peritoneum were present.

Such examinations have been much more frequently made of the urine, sputum, stomach-contents, feces, and vaginal discharges in the hope of establishing at the bedside the diagnosis of new growth, and not a few cases have been reported in which a correct diagnosis was made from the presence of tumor-cells or tumor-tissue in these excretions and secretions. Though in these days, when exploratory aspiration of almost every case of pleural or peritoneal effusion is made as a matter of course, and when the centrifugating-machine is so frequently utilized in the examination of the sediment, few cases of malignant growth diagnosed in this way have been reported. This seems

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strange when one considers the large number of cases of ascites due to peritoneal metastases in ovarian and gastric carcinoma, and the frequent cases of pleuritic effusion due to secondary carcinoma of the pleura following primary tumors of the mammary gland, etc.

It is evident that the possibility of diagnosticating new growths from the microscopic examination of effusions before a successful clinical diagnosis can be made would be a very important advance. The question then stands, To what extent is it possible, from the examination of the cellular elements of effusions, to establish the diagnosis of new growth of pleura or peritoneum?

The usual examination of the sediment of these fluids is confined to the direct microscopic examination of the fresh specimen, or to the examination of stained preparations for bacteria. In the majority of cases the search is limited to leucocytes and red blood-cells; and more emphasis is laid upon these than upon the character of other cells which may happen to be present. In addition to the blood-corpuscles, note is also made of endothelial cells, fat drops, fatty acid crystals, Charcot-Leyden crystals, cholesterin, pigment, fibrin threads, micro-organisms, and foreign material.

The presence of large numbers of large polymorphous cells, having numerous vacuoles or containing fat droplets, has led to the assumption in many cases that these cells were carcinoma cells, but from the fact that the endothelial cells in effusions exhibit such diversity of size and shape, and show also a similar degree of vacuolation and fatty degeneration, some

investigators have declared it impossible to diagnosticate with certainty the existence of a new growth unless bits of tissue showing definite structure can be found.

Quincke[1] endeavored to establish the principle that carcinoma cells can be distinguished from endothelial cells by their size, their number, their grouping into masses, and perhaps by their glycogen reaction. Later Rieder,[2] after a careful study of carcinoma cells in peritoneal and pleuritic fluids, concluded that the most important differential point between them and endothelial cells is in the large number of mitoses, especially asymmetrical division forms, which are found in the cells of tumors and not at all, or to a very slight degree in endothelial cells. The finding of many cells showing division figures he believed to speak conclusively for malignant growth. Neelsen, quoted by Rieder in the same article, diagnosticated carcinoma of the kidney from bits of tissue discharged in the urine, and which contained cells showing many asymmetrical mitoses.

Since Rieder's article, I have not been able to find any work bearing upon this point. The tumors which have been diagnosticated by a microscopic examination of cells found in effusions have been in all cases carcinoma, or, as in Rieder's case, atypical growths (*sarcoma carcinomatosum*), probably a mixed tumor arising from an ovarian teratoma. I have not been able to find any statement of a typical sarcoma of the peritoneal or pleural cavity, diagnosticated from the cells found in the effusion, but I have not been for-

[1] *Deutsch. Archiv. f. Klin. Med.*, vol. xxx.
[2] *Ibid.*, vol. liv.

tunate enough to secure all of the literature on primary endothelioma of the pleura, so that my search must be looked upon as incomplete. The evident rarity of such cases makes the report of the one which came under my observation some time ago very important because of its bearing upon the question of diagnosis. As far as I know, it is the only case in which sarcoma of the pleura has been correctly diagnosticated by an examination of the pleuritic exudate.

I am not at liberty to give the full clinical history of the case, my connection with it being limited to the examination of the effusion and the material obtained at the autopsy. The most important facts are as follows:

X., a German, male, about forty-five years of age, gave an indefinite history of dyspnea, pain in the right side of the thorax, cough, and progressive weakness. He also had irregular fever. The exact duration of these symptoms could not be ascertained because of the clouded mental condition of the patient when first seen.

The physical examination showed increased fulness of the right side of the thorax, with entire absence of movement. There was slight bulging in the fourth and fifth intercostal spaces between the nipple and sternal lines on the right side. There was a weak apex-beat in the left anterior axillary line in the fifth interspace. Vocal fremitus was absent over the right side. There was no friction fremitus. On percussion, dulness was found below the fourth rib on the right, rising to the level of the second rib when in a sitting position. Above this, there was dull tympanitic resonance. Over the area of dulness there was no breath-sounds and no adventitious sounds. Above the second rib there were faint blowing breath

sounds. The voice-sounds were only faintly transmitted above the second rib.

A diagnosis of pleurisy with effusion was made, the patient was aspirated, and the fluid sent to the pathologic laboratory for examination.

Pleuritic Exudate.—The fluid was brownish-red in color, with many yellowish or grayish flakes which settled quickly after agitation. The fluid was thick, but the amount obtained was not sufficient for the estimation of its specific gravity. On standing, fibrin was formed. The fluid coagulated solidly on boiling. The fresh sediment was examined, numerous stains and reagents being applied. Cover-glass preparations were made and a portion of the sediment was hardened for future examination.

The examination of the sediment, stained by allowing a drop of dilute methylene-blue solution to run under the cover-glass, showed the field to be full of spindle-cells of about the same shape and size, mostly single, but lying also in groups. There were numerous red blood-cells, leucocytes (mostly lymphocytes), fibrin threads, blood-pigment, and an abundance of fine granules, supposed to be cell *débris*. The leucocytes were not present in such numbers as to admit of the fluid being called purulent. Endothelial cells were present in only a very small number. They showed various degrees of vacuolation.

From the great number of spindle-cells present, the diagnosis of small spindle-cell sarcoma was made. The diagnostic points considered were the number of the cells and their character. The one alternative set against this diagnosis was a pleuritic effusion con-

taining large numbers of fibroblasts, but the regular size and shape of the cells were opposed to this view.

The patient gradually became worse. A rapidly progressing anemia and weakness, with constant delirium, were the most marked symptoms up to the time of death. The bulging on the right side between the nipple and sternal lines became more prominent before death.

The *post-mortem* examination was held four hours after death. The subject was very anemic and much emaciated. The pathologic conditions were confined to the thorax. The right half of the thoracic cavity was filled with a thick brownish-red effusion containing many large flakes and stringy masses. To these, blood-clots were attached. There were also large blood-clots floating in the fluid. The entire surface of the mediastinal pleura and of the anterior parietal pleura as far as the anterior axillary line was covered by a velvety growth; in some places the surface of the growth was covered by long strings of fibrin and blood-clot, firmly adherent to the tumor mass. In many areas the tumor itself consisted of long strings extending out into the pleuritic cavity. The greatest thickness of the growth (about three inches) was at the level of the fourth and fifth intercostal spaces between the right nipple and sternal lines, corresponding to the area of prominence in the chest-wall. The right lung was completely atelectatic; the visceral pleural was covered with fibrin, but there were no evidences of a new growth. The heart was pushed to the left, the right edge being at the left sternal line. The left lung and pleura were

normal, as were also the pericardium and heart. No metastases were found.

Tumor.—The tumor was mottled red and grayish-white. It was so soft that it could easily be crumbled between the fingers, and so fragile that it could hardly be cut without falling to pieces. The surface was uniform, homogeneous, without stroma, but rich in large blood-vessels, having very thin walls. There were numerous hemorrhagic areas, also areas of necrosis, grayish-yellow in color. In the stringy areas, the blood-vessels were surrounded by the grayish-white tissue of the tumor, giving to the naked eye the appearance of a perivascular growth.

Scrapings were made from the freshly cut surface of the tumor, and it was found to consist of medium-sized spindle-cells like those found in the effusion. The fluid obtained from the thoracic cavity was very rich in the same cells, so rich that it was not necessary to collect the sediment for examination. The specific gravity of the fluid was not taken.

Pieces of the tumor were hardened in alcohol and Müller's fluid. Sections were prepared from these, and the growth was found to consist of spindle-cells grouped about the large but thin-walled blood-vessels. Only a single layer of endothelium separated the blood from the cells. That the tumor-cells arose from the endothelium there can be no doubt; they were crowded more closely just around the endothelium, and here the nuclei stained more deeply than those away from the vessels. In specimens hardened in alcohol, dividing endothelial cells were seen, and in some cases the cells grew into the lumen, forming buds on the inner wall of the vessels. In

other cases, free masses of cells were found in the vessels. In the stringy areas covering the surface of the growth, all stages of development of the tumor tissue could be found, from the small capillary growing out into the fibrin with only a single layer of endothelium forming its walls and with no tumor tissue about it, up to the large blood-vessel surrounded by a large cylindric mass of cells. Throughout the tumor the structure was essentially perivascular, so that the tumor consisted of cellular cylinders surrounding the blood-vessels. Mitoses were abundant throughout; for the most part they were symmetrical.

From its histologic structure the tumor should be styled a spindle-celled hemangiosarcoma; from its origin it should be classed with the endotheliomata.

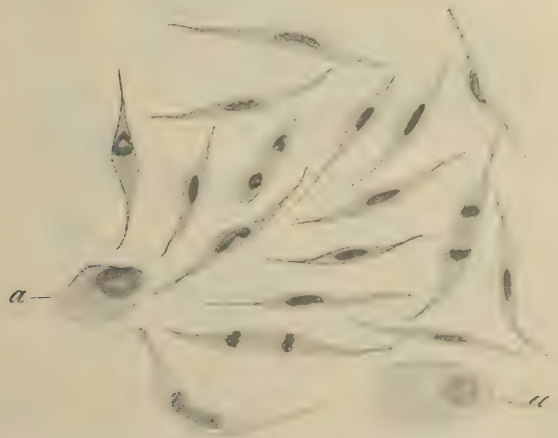
The hardened cover-glass preparations of the sediment were not examined thoroughly until some time afterward. These were stained in hemalum and examined with an oil-immersion lens. The finer structure of the cells was then carefully studied. The cells were spindle-shaped with rather long and slender polar processes which did not branch as is commonly the case with the spindle-cells found in inflammatory exudates. The nucleus stained rather heavily; was oval, as a rule, but in many cells was slightly curved. The chromatin was very abundant, but had a very simple structure. Numerous mitoses were found, but in all cases they were regular and symmetrical. They showed all stages of development.

As a rule, the cells were found singly, but groups were very common. They did not contain vacuoles, neither was any vacuolation of the nucleus observed. The rather abundant protoplasm was finely granular.

The epithelioid appearance of the nucleus so common to fibroblasts was not seen. Numerous necrosing cells were found, the protoplasm being more coarsely granular and the nucleus staining very poorly or not at all.

The pleural endothelial cells were relatively scanty. They were very irregular in size and shape, and showed various degrees of vacuolation. They pre-

FIG. 1.



Cells from effusion in primary sarcoma of the pleura. (*a*) Endothelial cells, all the others are tumor-cells, some showing cell division. (One-twelfth oil-immersion lens; ocular No. 2.)

sented no characteristics differing from the same cells found in ordinary pleuritic effusions.

In Fig. 1 the character and relative proportion of the cellular elements (blood-cells excepted) of the effusion in this case are shown.

Since the examination of this case I have made a study of the cells found in the sediment of the exu-

date in a large number of cases of diseased conditions of serous membranes—pleura, peritoneum, and pericardium. A description and comparison of the cells found under different conditions may be very valu-

FIG. 2.

Endothelial cells from sediment of effusion in early stage of acute serous pleurisy. (One-twelfth oil-immersion lens; ocular No. 2.)

able in itself and of aid in establishing a basis for diagnosis, if such be possible. The specimens were taken from cases in which the diagnosis was confirmed *post-mortem;* in some instances the fluid was obtained directly from the body-cavities, in others by puncture previous to death and also at the *post-mortem* examination. The cells were examined fresh, and fixed cover-glass preparations were made according to the method usually employed for the examination of

blood. The cleaned cover-glasses were spread with a thin film of the sediment, allowed to dry in the air for a few minutes, and then fixed in a mixture of equal parts of absolute alcohol and ether (one to two hours in the fixing fluid is sufficient). After fixing, the covers were dried in the air and stained at convenience. Hemalum or hematoxylon was the stains used most frequently.

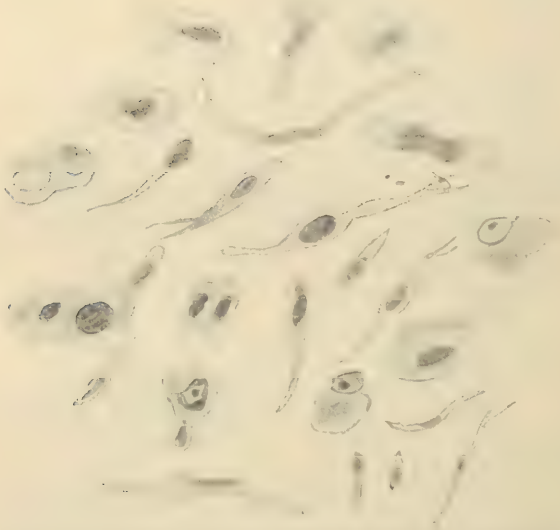
Acute Serous Pleurisy (Fig. 2).—The fluid was obtained in this case on the second day of the disease. It was clear, pale yellow, and contained numerous small whitish particles. These, when examined microscopically, were found to be masses of endothelial cells. From the large number of these desquamated groups of cells the pleurisy might be styled as desquamative. It is, however, the rule to find these in the very early stages of pleurisy. In these groups of cells the cell-membranes could not be made out. The cells were also found in great numbers isolated or in smaller groups of two or three.

As seen in Fig. 2, the cells were large, irregularly oval or round, and had an oval nucleus which stained less heavily than the nuclei of leucocytes or fibroblasts. They were for the most part vacuolated, the vacuoles being due to hydropic degeneration and not to fatty change. Some of the nuclei were also vacuolated. In many cases the vacuole occupied the entire cell, with the exception of the nucleus. In some cases the nuclei were partially extruded from the cell. Though the polymorphic character of the cells was very striking, no spindle forms were found in the early stage of simple pleurisy, though in the later

stages they become abundant. No mitotic forms were observed.

Acute Fibrinous Pleurisy (Fig. 3).—The effusion of both early and late stages of fibrinous pleurisy was examined. In all cases the fluid was cloudy, light

FIG. 3.

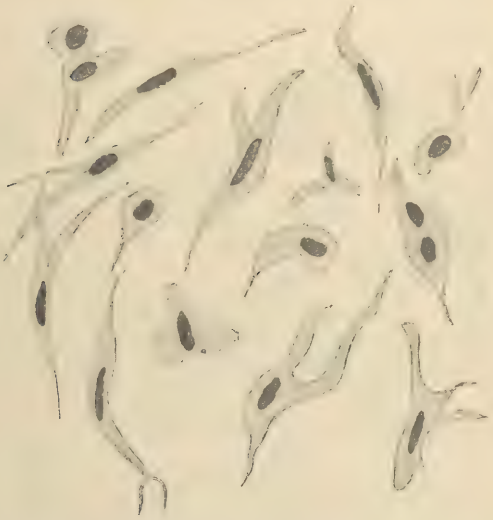


Cells from the sediment of acute fibrinous pleurisy, third week. Endothelial cells and various forms of fibroblasts. (One-twelfth oil-immersion lens; ocular No. 2.)

yellow, and contained numerous flakes and strings of fibrin. The pleuræ were covered by a thick layer of stringy fibrin. In both early and late stages the sediment contained vacuolated endothelial cells and numerous irregular spindle cells, having in many cases finely branched polar processes. These

cells had nuclei which stained more deeply than the endothelial cells, but in some cases they were epithelioid in character. Some of the nuclei of these irregular cells were vacuolated. In the early stage

FIG. 4.



Cells, probably fibroblasts wholly, from the sediment of pericardial fluid in the third week of acute fibrinous pericarditis. (One-twelfth oil-immersion lens; ocular No. 2.)

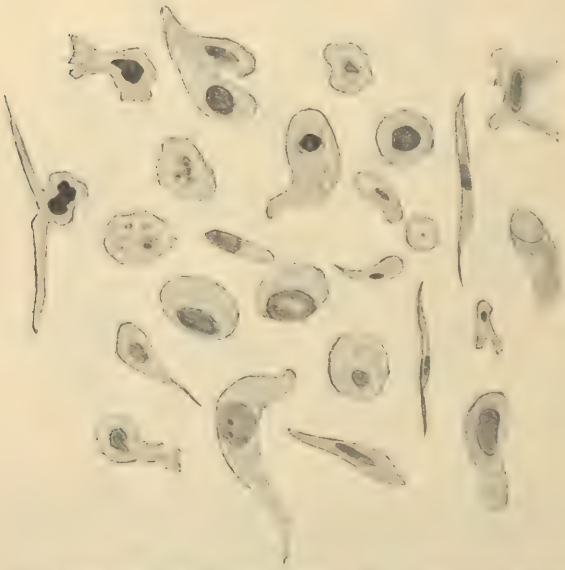
the endothelial cells predominated, but in the older cases of fibrinous pleurisy the spindle forms were much more numerous. They are to be looked upon, I think without doubt, as fibroblasts. No mitoses were found in these cells.

Tuberculous Pleurisy.—The exudate was obtained *post-mortem*. It was fibrinous, and similar in character to that found in simple fibrinous pleurisy. The

sediment of the fluid differed in no respect from that shown in Fig. 3, being made up of endothelial cells and fibroblasts. No mitoses were found.

Acute Fibrinous Pericarditis (Fig. 4).—The case examined was seen *post-mortem*, death having oc-

FIG. 5.



Cells from scraping of normal pleura. Endothelial cells, with a few connective-tissue cells from basement structure. (One-twelfth oil-immersion lens; ocular No. 2.)

curred during the third week. Both layers of the pericardium were covered by a thick layer of fibrin; in many places there were fresh adhesions which were easily separated by the fingers. There was a small quantity of thick grayish fluid between the

layers. On examination, no endothelial cells were found in this fluid, but numerous fibroblastic forms. These were much more branching than the cells found in the pleuritic exudates. No mitoses were found.

Scraping from Normal Pleura (Fig. 5).—For the sake of comparison, the cells obtained by scrapings from normal pleuræ were also studied. The surface of the membrane was gently scraped with the edge of a sharp knife so as not to loosen the cells of the basement structure. As seen in Fig. 5, the cells obtained in this manner are almost wholly characteristic polymorphic endothelial cells; the few spindle-cells found were doubtless from the basement connective tissue.

After a study of the sediment of many cases of effusion into peritoneal, pleural, and pericardial cavities, the following points seem to me to be worthy of emphasis:

1. In all cases of this kind, when fluid can be obtained by exploratory puncture, cover-glass preparations should be made by fixing in absolute alcohol and ether as described above. This should be done immediately after the withdrawal of the fluid from the body in order that the mitoses may be preserved.

2. In early stages of simple pleurisy the sediment contains endothelial cells and no fibroblasts. The endothelial cells may be desquamated in large pieces.

3. In fibrinous pleurisy, tuberculous or septic, the sediment contains, in addition to endothelial cells, numerous fibroblastic forms. In later stages, when adhesions are forming, the endothelial cells may be entirely absent, and only fibroblasts be found.

4. In the diagnosis of sarcoma of serous cavities, the character and number of the cells and the presence of numerous mitoses are the points upon which the diagnosis must be based. It is, of course, evident that the quickly growing and soft forms of sarcomata are the ones most apt to lead to the presence of cells in the fluid. The tendency of all sarcomata to break down after reaching a certain growth makes it extremely likely that in most cases free cells will be found. The diagnosis of spindle-celled sarcoma is easy, from the occurrence of large numbers of spindle-cells of similar size and shape, showing fewer branching processes than fibroblasts, and containing more mitoses. In the round-cell forms, the tumor cells are to be distinguished from the endothelial cells by their size, character of nucleus, and the relation of the nucleus to the protoplasm. The presence of mitotic forms will again be the most important point; in the small round-cell sarcoma, these are not so easily seen. The greatest difficulty will be in the differentiation of the cells of a polymorphus-celled sarcoma from the fibroblastic forms found in fibrinous exudates. Aside from the general character of cell and nucleus, the presence of division forms must in all cases be looked upon as being the most important point.

In conclusion, therefore, the presence of numerous cell-division forms in the cells of the sediment of serous exudates may be taken as strong (perhaps conclusive) evidence that the effusion is due to the presence of a new growth, inasmuch as mitoses are but rarely found in the cells of purely inflammatory exudates.

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